REMARKS

Claims 1-32 were pending in the present application. Claim 20 has been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claim in other applications. The Examiner has withdrawn claim 32 from consideration, alleging that claim 32 is drawn to a non-elected invention. Applicants respectfully submit that, for the reasons provided below, claim 32 is not drawn to a non-elected invention, and therefore claims 1, 2, 6-19, 21 and 32 should be under consideration in the present application.

Claim 1 has been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. More specifically, Claim 1 has been amended to recite "wherein the heat shock protein is not hsp60, and wherein the heat shock protein is not cpn10." Claim 1, as amended includes, in part, the language of now-canceled claim 20. Support for this amendment is found in the specification as filed, at page 7, lines 27-28. The present amendment is fully supported by the specification as filed and no new matter has been added.

Claim 32 Is Not Drawn to a Non-Elected Species

Claim 32 has been withdrawn from consideration by the Examiner under 35 U.S.C. §1.142(b), as allegedly drawn to a non-elected invention. At page 2 of the Office Action, the Examiner contends that claims 1 and 32 are drawn to different inventions because claim 1 "is drawn to a method employing a single hsp-antigen complex" while claim 32 "is drawn to a method employing a purified population of heat shock protein (HSP) - antigen complexes."

With respect to the propriety of the withdrawal of claim 32 under 35 U.S.C. § 1.142(a), Applicants respectfully direct the Examiner's attention to M.P.E.P. § 806.03, which reads as follows:

> Where the claims of an application define the same essential characteristics of a *single* disclosed embodiment of an invention, restriction therebetween should never be required. This is because the claims are but different definitions of the same disclosed subject matter, varying in breadth or scope of definition.

The Restriction Requirement imposed in the Office Action mailed January 3, 2001, defined Invention I, which was elected by Applicants, as drawn to "treating with HSP

complexed with antigen." Invention I includes independent claim 1 which recites "administering ... a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide." Claim 32 depends on claim 1 and recites "wherein said composition comprises a purified population of complexes."

Claim 32 depends upon claim 1and therefore the invention defined by claim 32 necessarily falls within the scope of the broader claim 1. Applicants further note that claim 1 is not limited to treatment with a single hsp-peptide complex as suggested by the Examiner. Claim 1 recites administration of a composition comprising a purified hsp-peptide complex and therefore encompasses administration of a composition comprising more than one (*e.g.* a purified population) of hsp-peptide complexes.

Claim 32 provides a variation on the breadth and scope of the invention of claim 1. Consequently, restriction of claim 32 should not be required. Applicants also assert that, pursuant to M.P.E.P. § 803, the subject matter of claim 32 can be examined together with that of claims 1, 2, 6-19, and 21 without imposing a serious burden on the Examiner. That is, Applicants respectfully submit that a search for prior art for claims 1, 2, 6-19, and 21, would necessarily yield any prior art for claim 32. Accordingly, Applicants respectfully request reconsideration of the withdrawal of claim 32 under 37 C.F.R. § 1.142(b) by the Examiner, and rejoinder of claim 32 to the pending claims of the above-captioned patent application.

The Rejection Under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claims 16-18 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. On page 2 of the Office Action, it has been alleged that the recitation of "the amount of the heat shock protein present in the complex is in the range of 5 μg to 5000 μg," "100 μg or more," or "200 μg or more," does not provide a specific dosage or dosage range. The Examiner further contends that "recitation of an amount in the composition alone does not disclose the amount given to the subject." Applicants, respectfully, do not agree.

Claim 1 recites "administration of a composition" while claims 16-18, which depend on claim 1, recite the range for the amount of hsp-peptide complex present in the composition of claim 1 that is administered. Consequently, the amount of hsp-peptide

complex administered, *i.e.* the dose, *is* the amount of hsp-peptide complex present in the composition. The amount need not be recited in terms of a concentration rather than weight. It is well within the routine skill of one skilled in the art to calculate weight from concentration and *vice versa*.

Consequently, Applicants respectfully submit that recitation of "the amount of the heat shock protein present in the complex is in the range of 5 μg to 5000 μg," "100 μg or more," or "200 μg or more," in claims 16-18 is not indefinite, and does teach those of skill in the art the proper dose of hsp-peptide complex to for use in the claimed method. Accordingly, Applicants respectfully request that the rejection of claims 16-18 under 35 U.S.C. § 112, second paragraph, be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 1-2 and 6-21 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over WO 95/15338 (hereafter "the '338 publication") and U.S. Patent No. 5,993,803 ("the '803 patent"), in view of U.S. Patent No. 5,750,119 ("the '119 patent") and Cohen (1992), "Autoimmunity to hsp65 and the Immunologic Paradigm," in Advances in Internal Medicine, 37: 295-311 (Mosby - Year Book Inc.) ("Cohen").

At page 4 of the Office Action the Examiner alleges that it would have been obvious to one of ordinary skill in the art to substitute hsp70, hsp90, and gp96 for the heat shock proteins recited in the methods of the '338 publication (comprising administration of cpn10) and the '803 patent (comprising administration of hsp60) in an attempt to arrive at the presently-claimed invention. The Examiner contends that motivation for this substitution would be based upon an asserted "interchangeability of heat shock proteins" allegedly taught by the '119 patent and Cohen. The Examiner further contends that since two heat shock proteins (cpn10 and hsp60) had been shown to reduce graft rejection, one of ordinary skill would reasonably expect other "interchangeable" hsp to be useful for reducing graft rejection since this would only represent "substituting equivalents for the same purpose." Applicants, respectfully, do not agree.

Applicants respectfully submit that the references cited by the Examiner (Cohen and the '119 patent) would not provide one of ordinary skill in the art with motivation to substitute other heat shock proteins for those heat shock proteins explicitly recited in the

methods of the '338 publication and the '803 patent. That is, Cohen and the '119 patent do not teach or suggest that heat shock proteins are interchangeable with one another. Applicants respectfully submit that the Examiner's basis for the rejection involves the impermissible use of hindsight gleaned from Applicants' own specification.

Cohen does teach that there is significant evolutionary conservation of amino acid sequence homology within an hsp subfamily, even across species boundaries:

> [m]olecules of hsp constitute a family of proteins divided into subfamilies named for their approximate molecular masses in kilodaltons: hsp90, hsp70, hsp65(also termed hsp60), and other, lower-molecular-weight proteins. Members of each hsp subfamily are produced by widely different creatures. Nevertheless, they are characterized by high degrees of sequence homology (page 297, last paragraph).

However, Cohen does not suggest that there are comparable similarities between members of different hsp subfamilies. In fact, a BLAST search has revealed that there is little to no significant sequence homology between members of different hsp subfamilies (*see* Exhibit 1, which provides the results of amino acid sequence comparisons between the following representative members of different heat shock protein subfamilies: cpn10, GroES, cpn60, GroEL, hsp70, hsp90, and gp96). [1]

Moreover, the teaching of Cohen is limited to hsp65 (also termed hsp60; see *e.g.* Cohen at page 297, last paragraph) as an autoantigen and the role that autoimmune responses to hsp65 may play in autoimmune disease. That is, Cohen is only directed toward elucidation of the hypothetical relationship between autoimmune response to hsp65 and, *e.g.*, autoimmune insulin-dependent diabetes mellitus (IDDM). The only other autoantigen even mentioned in Cohen in this context (*i.e.* autoimmune IDDM) is glutamic acid decarboxylase, which is not unique to pancreatic cells attacked in autoimmune IDDM (page 304-305). Accordingly, Cohen cannot be construed as teaching or even suggesting interchangeability of heat shock proteins since the only hsp mentioned in the context of being an autoantigen is hsp65. Similarly, as discussed below, the '803 patent, of which Dr. Cohen is an inventor, is

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[1] These sequence comparisons were carried out using pairwise protein BLAST comparisons (pblast), available at www.ncbi.nlm.nih.gov/BLAST which is described in Tatusova *et al.* (1999) "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences," *FEMS Microbiol. Lett.* 174: 247-250. Default parameters were used except the comparisons were done without use of the "Filter" option, which masks segments of the query sequence having low compositional complexity.

also limited to disclosure of an alleged method for reducing graft rejection that depends specifically upon down-regulating the autoimmune response to hsp60. The '803 patent does not teach or suggest that an autoimmune response to any other hsp even exists, much less down-regulating such an autoimmune response.

Similarly, although the '119 patent may suggest that hsp70, hsp90, and gp96 function in a similar manner in the method disclosed therein, which is for treating cancer, the disclosure of the '119 patent does not support the general inference that hsps are interchangeable for all purposes.

The '119 patent discloses that hsp-peptide complexes can be isolated from a specific tumor and used to induce an immune response against that tumor (column 4, lines 1-7, column 5, lines 51-55, and column 10, line 65 to column 11, line 2) but not against an antigenically-distinct tumor (column 7, lines 2-10). Moreover, hsp-peptide complexes isolated from normal cells do not induce an anti-tumor immune response (column 7, lines 2-10). The '119 patent discloses that the anti-tumor activity of hsp-peptide complexes isolated from a tumor is a reflection of the immunogenicity of tumor-specific peptides non-covalently bound to the heat shock proteins and is not a reflection of the antigenicity of the heat shock proteins *per se* (column 1, lines 61-67). More specifically, the '119 patent discloses that heat shock proteins such as hsp70, hsp90, and gp96 each form non-covalent complexes with peptides *in vivo*, and that those complexes can be used to induce an immune response against cells expressing those peptides (column 8, lines 41-46).

Therefore, Applicants respectfully submit that the '119 patent discloses that distinct heat shock proteins, *e.g.*, hsp70, hsp90, and gp96, have a similar function, *i.e.* the ability to form non-covalent complexes with peptides, which complexes can be used for treating and preventing cancer by inducing an immune response against the complexed peptides. However, the existence of this one shared function, without more, cannot be used as a basis to infer that these distinct heat shock proteins are interchangeable with one another for the purpose of treating or preventing graft rejection, where an immune response is being inhibited.

Therefore neither Cohen nor the '119 patent, either alone or in combination, support the Examiner's inference that heat shock proteins were known to be interchangeable with one another for the purposes recited in the claimed methods. Accordingly those of

ordinary skill in the art at the time of the present invention would not have been motivated to substitute other heat shock proteins, particularly hsp70, hsp90, and gp96, for the protein recited in the method of either the '338 publication or the '803 patent, in view of Cohen and the '119 patent.

At page 4 of the Office Action, the Examiner contends that those of ordinary skill in the art would reasonably expect that heat shock proteins other than cpn10 and hsp60 could be used successfully in the methods of the '338 publication and the '803 patent, respectively, since this would only involve an obvious substitution of equivalents for the same purpose. Again, Applicants respectfully disagree.

Applicants first note that, based upon the reasons discussed above in the preceding paragraphs, one of ordinary skill in the art at the time of the present invention would not have deemed heat shock proteins from different families to be interchangeable with or obvious over one another with respect to methods for preventing or treating graft rejection. Applicants further note, based upon the reasons provided below, that (1) the '338 publication teaches that neither groES, a protein included within the term "cpn10," nor cpn60 could be substituted for rat cpn10 in the method disclosed therein (that is, the '338 publication teaches that GroES and cpn60 are not equivalents of cpn10); and that (2) the teachings of the '803 patent are limited to hsp60 for use in the method disclosed therein (as discussed in the following section directed toward the teachings of the '803 patent).

The '338 publication discloses that mammalian cpn10 has the same amino acid sequence as that of early pregnancy factor ("EPF") (page 5, lines 14-16), a protein that was known to have immunosuppressive activity (page 3, lines 1-3). The '338 publication further discloses that mammalian cpn10 displays the same biological activity as EPF (page 10, lines 11-14) as indicated in an *in vitro* biological assay reflecting the immunosuppressive activity of EPF (page 3, line 13 to page 4, line 9).

The '338 publication also discloses that the term "cpn10" encompasses, *inter alia*, prokaryotic groES (page 5, lines 27-31). Nevertheless, in contrast to the results obtained with mammalian cpn10, the '338 publication discloses that GroES (*E. coli* cpn10) and *E. coli* cpn60 (GroEL/hsp60) do not display the immunosuppressive activity (page 10, lines 14-19), as measured *in vitro*. Accordingly, Applicants respectfully submit the '338 publication

teaches that other heat shock proteins, including hsp60 and GroES, could not be substituted for mammalian cpn10 in the method disclosed therein for suppression of graft rejection; *i.e.* even hsp60 and GroES are not equivalents of cpn10.

The '803 patent alleges that suppression of autoimmunity to hsp60 results in a reduction of graft rejection (column 3, lines 28-33). The '803 patent also teaches that the desired suppression of autoimmunity to hsp60 is mediated by hsp60-specific T cells (column 8, lines 18 to 24), and that graft rejection can, therefore, be alleviated by administration of hsp60 in a carrier or adjuvant that induces tolerance to hsp60 (column 10, lines 10-17). Accordingly, the method for reducing the severity of graft rejection disclosed in the '803 patent requires specific down-regulation of the autoimmune response to hsp60 (*see e.g.* independent claim 1 of the '803 patent).

Applicants therefore respectfully submit that, in view of the specificity of the immune system, it would be unreasonable to those of ordinary skill in the art to expect that an hsp60-specific immune response could be suppressed by administration of hsps other than hsp60. Therefore, there would be no basis for a reasonable expectation that a heat shock protein other than hsp60 could be used successfully in the method of the '803 patent to treat or prevent graft rejection.

The method disclosed in the '803 patent is based upon the specific suppression of an autoimmune response to hsp60 *per se*, which could only be achieved by the administration of hsp60 or a molecule displaying the antigenicity of hsp60. Therefore, the combination of references offered by the examiner to suggest that the presently-claimed invention is obvious would not only necessarily change the principle of operation of the method of the '803 patent but would be predicted also to render the method of the '803 patent inoperative. Accordingly, Applicants respectfully submit that the proposed substitution of other heat shock proteins for hsp60 of the '803 patent in an attempt to arrive at the presently-claimed invention, reflects an improper combination of references. [2]

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[2] (*See* MPEP § 2143.01; *In re Gordon* 221 USPQ 1125, 1127 (Fed. Cir. 1984), indicating that even if it would be possible to modify a prior art reference to arrive at the claimed invention, the art must teach the desirability of that modification. Moreover, if the (continued...)

Therefore, at the time of the present invention one skilled in the art would not have expected, with a reasonable expectation of success, that the method disclosed in the '338 publication could be used with hsps other than mammalian cpn10 or that the method disclosed in the '803 patent could be used with hsps other than hsp60.

Applicants respectfully submit that, for the reasons provided above, one of ordinary skill in the art would not have been motivated to substitute other heat shock proteins for cpn10 in the method disclosed in the '338 publication or for hsp60 in the method disclosed in the '803 patent. Moreover, even assuming *arguendo* that there were any motivation to substitute other heat shock proteins in either the method of the '338 publication or of the '803 patent, one of ordinary skill in the art would not have had a reasonable expectation of success in the treatment and prevention of graft rejection. Therefore, Applicants respectfully submit that independent claim 1, and therefore [3] claims 2, 6-19, 21 and 32 dependent thereon, are not obvious over the combination of the '338 publication, the '803, Cohen, and the '119 patent. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 6-19, and 21 as obvious under 35 U.S.C. § 103 over the '338 publication, the '803, Cohen, and the '119 patent, be withdrawn.

CONCLUSION

Applicants believe that each ground for rejection of the pending claims has been successfully overcome or obviated. Accordingly, Applicants respectfully request that the rejection of claims 16-18 under 35 U.S.C. § 112, second paragraph, and the rejection of claims 1-2 and 16-21 under 35 U.S.C. § 103, be withdrawn. Applicants submit that the entire application in now in condition for allowance, early notice of which would be appreciated.

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[2] (...continued)
proposed modification would render the prior art inoperable for its intended purpose, then that art actually teaches away from the proposed modification; and *In re Ratti* 123 USPQ 349, 352 (CCPA 1959), indicating that a rejection is not proper if it is based upon a proposed combination of references that requires a change in the basic principles under which the cited art was designed to operate.)

[3] "Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious." *In re Fine* 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)

Should the Examiner not agree with Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

Date: September 9, 2002

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Enclosure

Application of: SRIVASTAVA

Application No.: 09/393,652 Group Art Unit: 1644

Filed: September 10, 1999 Examiner: G. R. Ewoldt, Ph.D.

For: METHODS AND COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF GRAFT REJECTION USING HEAT SHOCK PROTEINS

Attorney Docket No.: 8449-025-999

Confirmation Number: 3088

Appendix A: Marked-up Version of the Claims Amended Herein

Matter that has been deleted is enclosed in brackets, while that added is underlined.

1. (Twice Amended) A method of preventing or treating rejection of a grafted cell, tissue, or organ in a mammal comprising administering to the mammal a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, and wherein the heat shock protein is not hsp60 or cpn10.

Application of: SRIVASTAVA

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For: METHODS AND COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF GRAFT REJECTION USING HEAT SHOCK PROTEINS

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Appendix B: The Claims As They Will Be Pending Upon Entry of the Present Amendment Dated September 9, 2002

1. (Twice Amended) A method of preventing or treating rejection of a grafted cell, tissue, or organ in a mammal comprising administering to the mammal a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, and wherein the heat shock protein is not hsp60 or cpn10.

2. The method of Claim 1, wherein the heat shock protein is not an alloantigen of the grafted cells, tissue, or organ.

6. The method of Claim 1, wherein the grafted cell, tissue, or organ is skin, liver, kidney, heart, bone marrow, pancreas, lung, cornea, cartilage, or a cell derived therefrom.

7. The method of Claim 6, wherein the grafted cell or tissue is skin or a cell derived from skin.

8. The method of Claim 1, wherein the heat shock protein is mammalian.

9. The method of Claim 8, wherein the heat shock protein is human.

10. The method of Claim 8, wherein the heat shock protein is gp96.

11. The method of Claim 8, wherein the heat shock protein is hsp70.

12. The method of Claim 8, wherein the heat shock protein is hsp90.

13. The method of Claim 1 or 2, wherein the mammal is human.

14. The method of Claim 1, comprising administering the composition before the cell, tissue, or organ is grafted.

15. The method of Claim 1, comprising administering the composition after the cell, tissue, or organ is grafted.

16. The method of Claim 1 wherein the amount of the heat shock protein present in the composition is in a range of 5 μg to 5,000 μg.

17. The method of Claim 1, wherein the amount of the heat shock protein present in the composition is 100 μg or more.

18. The method of Claim 1, wherein the amount of the heat shock protein present in the composition is 200 μg or more.

19. The method of Claim 14, further comprising administering to the mammal a sample of cells or tissue obtained from the cell, tissue, or organ donor prior to administration of the heat shock protein.

20. Canceled.

21. The method of Claim 1, wherein the peptide is not a bacterial peptide.

32. The method of claim 1, wherein said composition comprises a purified population of complexes, each complex in said population consisting essentially of a heat shock protein non-covalently bound to a peptide, and wherein each peptide is independently selected from a population of different peptides.